NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

PHL-358-PHARMACOLOGY AND THERAPEUTICS-I

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Mechanisms of Pain and Nociception

• Nociception is the mechanism whereby noxious peripheral stimuli are transmitted to the central nervous system. Pain is a subjective experience, not always associated with nociception.
Mechanisms of Pain and Nociception

- Polymodal nociceptors (PMN) are the main type of peripheral sensory neuron that responds to noxious stimuli. The majority are non-myelinated C-fibres whose endings respond to thermal, mechanical and chemical stimuli.
Mechanisms of Pain and Nociception

• Chemical stimuli acting on PMN to cause pain include bradykinin, 5-HT, and capsaicin. PMN are sensitised by prostaglandins, which explains the analgesic effect of aspirin-like drugs, particularly in the presence of inflammation.

• Nociceptive fibres terminate in the superficial layers of the dorsal horn, forming synaptic connections with transmission neurons running to the thalamus.
Mechanisms of Pain and Nociception

- PMN neurons release glutamate (fast transmitter) and various peptides (especially substance P) which act as slow transmitters. Peptides are also released peripherally and contribute to neurogenic inflammation.

- Neuropathic pain, associated with damage to neurons of the nociceptive pathway rather than an excessive peripheral stimulus, is frequently a component of chronic pain states, and may respond poorly to opioid analgesics.
Fig 37.2 Summary of modulatory mechanisms in the nociceptive pathway.
Opioid Analgesics

• There are three main families of endogenous opioid peptides; these have analgesic activity and have many physiological functions, but they are not used as drugs.

• Opioid drugs include:
  – Phenanthrene derivatives, structurally related to morphine
  – Synthetic compounds with dissimilar structures but similar pharmacological effects
Opioid Receptors

• μ-receptors are thought to be responsible for most of the analgesic effects of opioids, and for some major unwanted effects (e.g. respiratory depression, euphoria, sedation and dependence). Most of the analgesic opioids are μ-receptor agonists.

• δ-receptors are probably more important in the periphery, but may also contribute to analgesia.

• κ-receptors contribute to analgesia at the spinal level, and may elicit sedation and dysphoria, but produce relatively few unwanted effects, and do not contribute to dependence. Some analgesics are relatively κ-selective.
Opioid Receptors

• σ-receptors are not true opioid receptors, but are the site of action of certain psychotomimetic drugs, with which some opioids interact.
• All opioid receptors are linked through G-proteins to inhibition of adenylate cyclase. They also facilitate opening of $K^+$ channels (causing hyperpolarisation), and inhibit opening of $Ca^{2+}$ channels (inhibiting transmitter release). These membrane effects are linked to the decrease in cAMP formation.
Morphine

- Pharmacological effects and Mechanisms

  CNS effects
  - Analgesia: increasing tolerance of pain are the most prominent effects. Therefore, help patients to eliminate dysphoria, anxiety. Consciousness is not lost, and the patient can usually still locate the source of pain.
Morphine

CNS effects

- Respiratory depression and suppression of cough: reducing the responsiveness of the respiratory centers in the brain stem to blood levels of carbon dioxide and inhibiting directly the respiratory center.
Morphine

CNS effects

– Nausea and vomiting: stimulating the chemoreceptor trigger zone. In most cases, after therapeutic dose, subsequent doses of morphine do not produce vomiting.

– Miosis: pinpoint pupils are indicative of toxic dosage prior to asphyxia. It can be block with atropine.
Morphine

**Cardiovascular effects:**
– Orthostatic hypotension can occur due to vasomotor medullary depression and histamine release.

**Gastrointestinal effect:**
– Reduces gastrointestinal motility, causing constipation
– Decreases biliary and pancreatic secretions.
– Constriction at the spincter of Oddi causes an increase in biliary pressure.
Morphine

Other systemic effects:

– Increases detrusor muscle tone in the urinary bladder, producing a feeling of urinary. Vesical sphincter tone is also increased, making voiding

– Inhibits the cellular immunity and humoral immunity, which is significant in withdrawal syndrome and tolerant in chronic administration.
Pharmacokinetics of Morphine

- Is well absorbed from the gastrointestinal tract. However, the analgesic effect is greater when drug is administered intramuscularly or intravenously. It has a significant first-pass effect.
- Morphine is metabolised to morphine-6-glucuronide, which is more potent as an analgesic.
- Ninety percent of a given dose is excreted in the urine; the remaining 10% is excreted in the feces.
Therapeutic uses

- Analgesia, such as the relief of pain from myocardial infarction, terminal illness, surgery, biliary colic and renal colic (combined with atropine).
- Dyspnea due to pulmonary edema because of sedative, vascular dilation and inhibition of the respiratory centers responsiveness to CO$_2$.
- Treating severe diarrhea because of constipating effects.
- Treating cough (usually insteaded by codeine).
Adverse effects

- Respiratory depression is the most important effect.
- Nausea and sometimes dysphoria can occur.
- Increase biliary tract pressure.
- Allergic reactions.
- Bronchoconstrictive action.
- Tolerance and Dependence
Tolerance and Dependence

- Tolerance develops rapidly, accompanied by physical withdrawal syndrome.
- The mechanism of tolerance may involve adaptive up-regulation of adenylate cyclase. It is not pharmacokinetic in origin and receptor down-regulation is not a major factor.
Tolerance and Dependence

• Dependence comprises two components:
  (a) physical dependence (somewhat resembling severe influenza, with yawning, pupillary dilatation, fever, sweating, piloerection, nausea, diarrhoea and insomnia), associated with the withdrawal syndrome, lasting for a few days;
  (b) psychological dependence, associated with craving, lasting for months or years.
Tolerance and Dependence

- Weak, long-acting μ-receptor agonists, such as methadone, may be used to relieve withdrawal symptoms.
- Certain opioid analgesics, such as codeine and pentazocine, are much less likely to cause physical or psychological dependence.
Contraindications and cautions

- Use in patients with head injuries
- Use during pregnancy
- Use in patients with impaired pulmonary function
- Use in patients with impaired hepatic or renal function
Codeine

- Although the pharmacologic effects of codeine are similar to those of morphine, it has about one-twelfth the analgesic potency of morphine.
- Be used mainly for cough suppressant and milder pain.
- It produces less sedation, respiratory depression, fewer gastrointestinal effects, and less addiction and withdrawal.
Synthetic analgesic: Pethidine

• It is very similar to morphine (one-seventh to one-tenth potent) in pharmacologic effects by μ-receptor agonists.

• Therapeutic uses: analgesic, cardiac asthma, sedation (decrease the dosage of anesthetic) and artificial hibernation.

• It has no gastrointestinal or antitussive action because of shorter-acting.

• Adverse effect: also causes respiratory depression and possesses addiction liability, although withdrawal effects are less severe than with morphine.
Methadone

- It is widely used as a means of treating morphine and diamorphine addiction because of its chronic and insignificant addiction.
Opioid receptor mixed agonists/antagonists

• Other drugs, such as nalorphine and pentazocine, produce a mixture of agonist and antagonist effects.
Opioid Antagonists

• Pure antagonists include naloxone (short-acting) and naltrexone (long-acting). They block $\mu$-, $\kappa$- and $\delta$ receptors more-or-less equally.

• Naloxone does not affect pain threshold normally, but blocks stress-induced analgesia, and can exacerbate clinical pain.
Opioid Antagonists

• Naloxone rapidly reverses opioid-induced analgesia and respiratory depression, and is used mainly to treat opioid overdose or to improve breathing in newborn babies affected by opioids given to the mother.

• Naloxone precipitates withdrawal symptoms in morphine-dependent patients or animals.
Clinical Use of Analgesic Drugs

• The choice and route of administration of analgesic drugs depends on the nature and duration of the pain.
• A progressive approach is often used, starting with nonsteroidal anti-inflammatory drugs, supplemented first by weak opioid analgesics, and then by strong opioids.
Clinical Use of Analgesic Drugs

• In general, severe acute pain (e.g. trauma, burns, post-operative pain) is treated with strong opioid drugs (e.g. morphine, fentanyl) given by injection.

• Mild inflammatory pain (e.g. arthritis) is treated with non-steroidal anti-inflammatory drugs (e.g. aspirin) supplemented by weak opioid drugs (codeine, pentazocine) given orally if required.

• Severe pain (e.g. cancer pain, severe arthritis or back pain) is treated with strong opioids given orally, intrathecally, epidurally or by subcutaneous injection.
Clinical Use of Analgesic Drugs

• Chronic neuropathic pain is often unresponsive to opioids, and treated with tricyclic antidepressants (e.g. amitriptyline), or other drugs, such as carbamazepine.